AD_____

GRANT NUMBER DAMD17-94-J-4475

TITLE: Effects of Meditation-Based Stress Reduction in Younger Women with Breast Cancer

PRINCIPAL INVESTIGATOR: James R. Hebert, Ph.D.

CONTRACTING ORGANIZATION: University of Massachusetts
Medical Center
Worcester, Massachusetts 01655

REPORT DATE: October 1998

TYPE OF REPORT: Annual

PREPARED FOR: Commander
U.S. Army Medical Research and Materiel Command
Fort Detrick, Frederick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 1998	Annual (30 Sep 97 - 29 Sep 98)

4. TITLE AND SUBTITLE
Effects of Meditation-Based Stress Reduction in Younger Women with Breast Cancer

5. FUNDING NUMBERS
DAMD17-94-J-4475

6. AUTHOR(S)
James R. Hebert, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Massachusetts Medical Center
Worcester, Massachusetts 01655

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Commander
U.S. Army Medical Research and Materiel Command
Fort Detrick, Frederick, Maryland 21702-5012

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200*

The Breast Research Initiative for DeterminiG Effective Skills for coping with Cancer (BRIDGES) consists of a prospective, randomized intervention trial with sixty women in each of three arms: 1) the UMASS mindfulness meditation-based Stress Reduction and Relaxation Program (SR & RP); 2) a nutrition education program (NEP) developed specifically for BRIDGES; and 3) a usual care control group. The 180 women under age 65 with Stage I or Stage II breast cancer enrolling into this randomized trial are being evaluated for: 1) psychological and behavioral indices of function and coping; 2) Quality of Life (QOL) measures; 3) compliance with the interventions and with medical treatment regimes; and 4) biochemical/immunological measures consisting of cytokines and melatonin. Analyses will be conducted to test hypotheses related to the three specific aims of the study: SR&RP effect on QOL; SR & RP & NEP effects on immune parameters; and durability/decay of intervention-related effects. As of 30 September 1996, the study had closely adhered to the Statement of Work agreed upon at the time the grant was awarded. 178 women were recruited and randomized into the study. Most subjects (90%) who have been randomized and begun the study have been retained. All data have been collected as per protocol stipulations.

14. SUBJECT TERMS
Breast Cancer

15. NUMBER OF PAGES
21

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

____ Where copyrighted material is quoted, permission has been obtained to use such material.

____ Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

____ Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

____ In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and use of Laboratory Animals of the Institute of Laboratory Resources, national Research Council (NIH Publication No. 86-23, Revised 1985).

__X__ For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

____ In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

____ In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

____ In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

PI - Signature

21 October 1998

Date

TABLE OF CONTENTS

INTRODUCTION

An increasing body of research literature has shown that psychological states have clear impact on recovery and quality of life in women with breast cancer. Psychosocial variables such as emotional expression, coping styles, and factors related to social support appear to have the most promise for improving quality of life and increasing the probability of prolonged survival. There also is a small body of evidence indicating that women with breast cancer receiving psychosocial interventions may have longer disease-free and total survival. Psychological distress seems to be particularly acute in younger women with breast cancer, a population that seems particularly amenable to psychosocial interventions. This is due, in part, to the fact that younger women with breast cancer tend to receive more aggressive treatment. It is often their first experience with serious illness and younger women tend to have more concern with issues related to body image and major disruptions to typically very busy lives.

In light of these findings, there is an important need for the development of cost-effective psychosocial interventions for women with breast cancer. A successful intervention will be one that can reduce emotional distress, promote effective coping with diagnosis and treatment for breast cancer, and be useful and adaptable to the diverse population of younger women with breast cancer. The current study seeks to adapt the University of Massachusetts Medical Center's Stress Reduction and Relaxation Program (SR&RP) for younger women with breast cancer. The SR&RP is a well-established intervention program with demonstrated effectiveness in improving emotional status and quality of life in individuals with a variety of serious medical problems. The program is educationally based and has been conducted in a variety of health care settings with diverse populations.

Our research addresses aspects of two of the fundamental research issues in psychosocial effects of breast cancer and the role of our well-recognized (but hitherto untested in this population of patients) SR&RP intervention in quality of life and status of immune parameters that may themselves be important in determining disease prognosis. Specifically, this research is designed to: 1) examine the psychosocial impact of breast cancer; and 2) identify techniques for delivering cost-effective care to facilitate recovery, improve immunological response, and improve quality of life after treatment for breast cancer.

Overall Goal

The primary goal of this proposal is to test the efficacy of the well-established, short-duration mindfulness meditation-based Stress Reduction and Relaxation Program (SR&RP) in women under 65 years old with newly diagnosed Stage I and Stage II breast cancer. The SR&RP intervention aims to influence a number of well-defined psychosocial factors which are suggested by a growing body of evidence as critically important for: adjustment to a potentially life-threatening diagnosis; enhancement of quality of life; and potentially, for enhancement of resistance to disease progression and

survival in women with breast cancer. The study will consist of a prospective randomized three-arm design with 60 women enrolled into each arm: 1) the SR&RP intervention, tailored to focus on issues specific to this population; 2) a nutrition education program (NEP) which will serve as an inactive attention control with regard to the psychosocial outcome measures and as a potentially active intervention with regard to effect on immune parameters (see Specific Aim 2); and 3) a usual care control group.

Specific Aim 1: To test the effect of SR&RP on Quality of Life (QOL), emotional awareness and expression, coping strategies and related perceptual and behavioral factors, and compliance with the intervention and with medical recommendations in women (under 65 years old) with newly diagnosed Stage I and II breast cancer. Because the SR&RP and NEP groups will have an equally intense group session component and the NEP group will receive none of the essential components of the SR&RP, the test between the two groups, SR&RP and NEP, will distinguish between the effect of the SR&RP intervention and non-specific group/therapist factors.

Primary Hypothesis: The SR&RP intervention will result in improved QOL and ability to cope, compared either to the NEP or to usual care alone.

Secondary Hypothesis: The SR&RP intervention will result in: a) improved perception of self and self in relationship to the world, as measured by increased self-esteem, sense of coherence, and decreased loneliness; b) a corresponding reduction in mood disturbance (e.g., anxiety and depression); c) increased use of active-behavioral and active-cognitive coping strategies, as measured by the Dealing with Illness Coping Inventory; and d) increased compliance with treatment regimens as compared to usual care alone.

Specific Aim 2: To test the relative effect of the SR&RP versus NEP and usual care on immune parameters specifically related to cytokines that activate Natural Killer (NK) cells and melatonin levels that may in turn affect response to breast cancer [Massion, 1995 #1390]. Because NK activity may be related to recurrence [Levy, 1991 #134] we have previously shown that low-fat diets enhance NK activity [Hebert, 1990 #313] and we have preliminary data that meditation may affect melatonin levels in women, we are particularly interested in relative differences between the two test groups, SR&RP and NEP, compared to usual care alone.

Specific Hypothesis: Relative to usual care, the SR&RP intervention will increase the immune responsiveness of Stage I and II breast cancer patients. This will result in an increase in the production of cytokines, e.g., Interleukins 2 and 4 (IL-2,4), which activate NK cells, and interferon (IFN)γ, which activates macrophages.

Specific Aim 3: To determine if the study effects (described in Aims 1 and 2), along with maintenance of the intervention practices, persist over 1-2 years of follow-up.

Specific Hypothesis: Psychosocial and immunological changes will be maintained over time and related to on-going practice of the SR&RP and NEP dietary practices, self-regulatory strategies and behaviors.

WORK ACCOMPLISHED

It is important to note that when the grant was written, we stated that women who were under fifty years of age would be entered into our study. We have extended this criterion to include any women who is under sixty-five years old at time of diagnosis with breast cancer. The reasons for extending the age requirement are as follows: 1) typically women work until they are sixty-five years old, which means they lead lives as busy as those of women under age fifty in fact, we find they often are busier in respect to career development; 2) we found that these women also have concerns with issues related to body image; and 3) we had no reason to believe that these women would not obtain the same benefits from the interventions. The age of 65 years provides a natural and culturally widely appreciated demarcation between early middle age, and its concomitant demands and pressures, and late middle age, with its progressive decline in terms of life pressures.

Because the Statement of Work contained in effect at the time the grant was awarded, provides the framework for all activities undertaken since that time, we employ it here as the outline of all progress.

Task 1: Run-in Phase. Months 1-3

a. Additional focus groups and preliminary data will be gathered as needed.

   Weekly meetings were held for the first 6 months of the study. These were always attended by the four site coordinators and two Co-Principal Investigators from the University of Massachusetts. In the first 3 months, other investigators (mainly oncologists and surgeons) also attended the meetings. At these sessions, recruiting protocols were developed and patient communication and other issues were discussed and resolved. It was determined that sufficient preliminary data were collected prior to the grant application process in order to guide planning of the recruitment protocols and data collection instruments. Therefore, additional focus groups were not held.

b. Based on focus group and preliminary studies, introductory and booster (therapy) sessions will be developed so that the content of the program will be most useful to younger women with early stage breast cancer.

   Introductory and booster sessions were developed. We determined that there would be two introductory sessions for the SR&RP intervention. At these sessions, women discussed their experience with breast cancer and started learning about mindfulness-meditation. There were an average of twelve women in each of these classes. The

size of the groups allowed them to support one another's experiences and enabled them to bond so that when they attended the SR&RP classes they were likely to know someone in their class. These sessions gave the women a chance to meet and talk with other women who were experiencing the same illness. It also allowed them to ask questions or talk about whatever was important to them. There were four booster sessions which were held after the standard SR&RP classes. At these sessions, women learned more about meditation and yoga, discussed their experiences in the SR&RP and continued to discuss their experiences with breast cancer. These sessions served to review and reinforce what they had learned in the SR&RP and gave the women a chance to talk about issues of personal concern to them.

c. The Nutrition Education Program will be developed using the recently funded Women's Health Initiative as an appropriate low-fat model.

The Nutrition Education Program (NEP) was to be developed using the recently funded Women's Health Initiative (WHI) as an appropriate low-fat model. It was decided that we could design and implement a low-fat intervention superior to that of the WHI. Therefore, we invested the necessary resources and developed a program specific to BRIDGES. The NEP consisted of an overview of diet and health with an emphasis on how change in diet can affect well-being and how it broadens rather than narrows dietary options. The program was held at a location close to the University of Massachusetts Medical School in Worcester and consisted of 14 weekly sessions each ninety minutes long. There was an additional session on a Saturday or Sunday which lasted six hours. The participants were asked to do various homework (cooking and nutrition) assignments which helped them to incorporate the program information into their daily life. At these classes the women did hands-on preparation and tasting of low-fat, high-fiber foods. They were taught alternative methods of creating and enhancing flavors including the use of spices and herbs. The transition to low-fat eating also entailed increased consumption of vitamins and minerals. The role of these nutrients plus various spices in health were discussed. The individuals assigned to this intervention developed personal eating plans and dietary goals so that they reduced the amount of fat in their diet to less than twenty percent of the calories that they eat.

d. Instrument material will be piloted and finalized, where appropriate. Reliability tests will be conducted when necessary.

Because all instruments had been validated and checked for reliability in previous studies it was not necessary to conduct separate reliability tests for BRIDGES. All instrument materials were piloted and finalized as stipulated in the protocol. Most of the instruments are being used in our other studies and all have performed well in previous tests of validity and reliability. We omitted the interviewer-administered questionnaires (i.e., the Hamilton Anxiety and Depression Scales) because they were redundant to other self-assessment data. Copies of these instruments were included in the appendix of the original submission and modified forms currently in use in the

study were included in the appendix of last year's annual report. Below is a list of instruments being utilized.

Baseline questionnaire Measures include: Background and Demographic Data: age; sex; marital status; education; number of children; number and dates of pregnancies; breast feeding history: (months for each child); and menopausal status (including surgical menopause). Personal Health History: present medical/psychiatric history and treatment (including history of exposure to estrogens, oral contraceptives, unusual menstrual problems). Family Health History: history of breast cancer; history of other cancers. General Self Care: sleep; exercise frequency; and smoking status.

Besides data collected on the baseline instrument we also administered these other questionnaires:

Beck Anxiety Inventory
Beck Depression Inventory
Sense of Coherence
Revised UCLA Loneliness Scale
Rosenberg Self-Esteem Scale
Functional Assessment of Cancer Therapy (FACT)
Mini-Mac Scale
Dealing with Illness
Marlowe-Crowe Social Desirability (MCSD) scale (Personal Reaction Inventory)
Symptom Check List
Social Readjustment Rating Scale
Social Approval
Seven Day Dietary Recall (7DDR)

e. An introductory video tape (to be used for recruitment) will be produced.

Dr. Ockene directed this task. During the weekly meetings (which were discussed in 1a) the purpose of the video, along with the content of the script, was discussed. The Project Coordinator and a representative from each site were videotaped. The video is five minutes long. It includes information about the funding source, why the study is important, and how the study is designed. It was shown to most of the women who were interested in joining the study. The video tape and script were included in the appendix of last year's annual report.

f. The Project Coordinator will be hired and trained in conducting phone and in-person interviews by Drs. Clemow and Massion.

The Project Coordinator, Susan Druker, was hired. Due to her skills in conducting interviews, the training session was not needed. Also, as noted above, we decided not to include in the battery of psychosocial instruments the Hamilton Anxiety Scale and

the Hamilton Depression Scale. Both of those scales are administered verbally. Ms. Druker worked with the three other site coordinators in developing numerous study protocols including ones for periodic interviewing.

g. A database to be used in the will be constructed.

This task has been completed. The biostatistician along with a research fellow developed a plan for our database. A research assistant, Jay Fowke, has been hired to work part time. He is at the University of Massachusetts pursuing a Ph.D. in Public Health.

h. Analysis of available run-in phase data will be done by Drs. Hebert and Massion. We have conducted process-related analyses (to assure data collection steps have occurred) and performed simple univariate analyses. Thus far all data are completed, within range, and have good internal logic. Jay's role is to develop a formal data management plan for BRIDGES. After identifying all the sources of data we are collecting, he created the data entry programs for all data not collected via optically scanned instruments. Along with the biostatistician he determined the location of data entry-files, the choice of data entry personnel, the timetable for data entry, quality assurance steps, and timing and the backup and archiving of the analytic data entry steps.

Task 2: Recruitment. Months 4-21:

a. 180 women (age <50 years) with Stage 1 or 2 breast cancer from Worcester, Ma and Providence RI will be recruited as participants for the study.

178 (99% of the recruitment goal) individuals have been enrolled into the study. As discussed previously, we extended the age eligibility to women who were diagnosed with Stage 1 or 2 breast cancer at age 65 or less. A patient brochure was developed along with a letter that is signed by one of their physicians in order to assist with recruitment.

18 (10%) have dropped out of our study. We estimated that our retention rate would be 80%. Our high retention rate is due to the positive response of our patients to this study.

b. Baseline measures will be taken on all study parameters as stated in the protocol.

A baseline questionnaire was developed as described in last year's report. The following anthropometric measures were taken at baseline: height; weight; sitting height; and waist and hip circumference. Blood also was drawn and a twenty-four hour urine was collected. The medical questionnaire was to be used to collect information on: date of first positive cytology or positive biopsy; if individual had

radiation, when and if there were major complications; what type of surgery was performed (i.e. lumpectomy alone, mastectomy, etc.); histology; tumor size; tumor grade; tumor differentiation; axillary nodes samples; estrogen/progesterone receptor concentrations; stage of breast cancer and information about their chemotherapy treatment. A nutritional assessment was completed by all participants. For this, we are using a seven-day diet recall(7DDR).

c. Study subjects will be randomized into one of the three arms of the study 1) Stress Reduction and Relaxation (SR&RP); 2) Nutrition Education Program (NEP), and 3) Usual supportive care(UC).

Study subjects were randomized into one of the three arms of the study 1) the Stress Reduction and Relaxation (SR&RP); 2) the Nutrition Education Program (NEP), and 3) Usual supportive care (UC). We call the UC arm, the Individual Approach Condition and state in our patient brochures that they choose whatever strategy to cope that they think is best for them. An eligibility requirement form that was developed continues to be used. Of the 178 subjects randomized 60 are in SR&RP, 59 are in NEP and 59 are in UC.

Task 3: Intervention. months 6-27;

a. Participants will become involved in the intervention arm to which they are randomized. The SR&RP and NEP will be given four times per year at UMMC.

The interventions were given three-times per year. Six interventions have been offered, all lasting 14 weeks. We decided to add another intervention in order to achieve our goal of recruiting 180 women. This decision was reached due to two of the participating institutions falling short of their recruiting goals. Each institution was to recruit 45 women. One institution, because of the distance to the University of Massachusetts Medical Center, only recruited 16 patients. The other institution which fell short of their goal recruited 30 patients. The women involved in SR&RP and NEP gave rave reviews of the interventions. We contact them on a monthly basis to obtain feedback and, without exception, everyone states very positive things about being involved in the study.

b. Just prior to the interventions (or time-controlled for the women randomized to usual care) all parameters (except immuno-endocrine measures and diet) assessed at baseline will be reassessed.

Because of budgetary restrictions prior to final approval, we reduced measurements from five to four times over the period of each woman's involvement. To make best use of these data, we decided that all baseline measures (see 2b) would be taken just prior to the interventions. Therefore, there was no need to reassess these measures

prior to the interventions. We have collected 177 baseline measures, 160 four month measures, and 123 one year measures and 39 two year measures so far.

c. The SR&RP group will receive the standard SR&RP segment plus additional therapy sessions for a total of fifteen sessions. The SP&RP group receive the standard SR&RP segment plus additional therapy sessions for a total of fifteen sessions. As stated previously, two introductory sessions plus four booster sessions are required for all women who enter the SR&RP arm of the study. For more information see 1b.

d. The NEP group will receive their intervention on approximately the same schedule as women in the SR&RP arm of the study.

The NEP group received their intervention at the same time as the women in SR&RP. Nutrition classes and SR&RP classes lasted for fourteen weeks and begin and end at the same time.

Task 4: Follow-up months 8-46;

a. All participants will be assessed just after the intervention (or time adjusted for all women in the UC) and at twelve months and twenty four months after recruitment. Assessment will include all the psychological and quality of life measurements, as well as immuno-endocrine parameters and the nutritional assessments. At twelve months melatonin will be assessed. Nutrition assessments will be made only at the twelve month and twenty four-month post recruitment points in order to account for seasonal differences in dietary intake.

All participants are assessed just after the intervention (or time adjusted for all women in the UC) and at twelve months and twenty-four months after baseline. Assessment includes all the psychological and quality of life measurements, as well as immuno-endocrine parameters and the nutritional assessments. At four and twenty-four months, melatonin is assessed. Nutrition assessments also are made at four months, twelve months, and twenty-four months after baseline. We decided to do the nutritional assessment at four months because the information gathered provides us with data as to whether women have changed their diet immediately subsequent to the intervention. Monthly phone calls also are utilized to gather data. It is during these phone calls that we check for compliance with the SR&RP protocol.

b. Ongoing data collection, review for completeness, and preliminary testing of study hypotheses will occur.

All site coordinators review the questionnaires which are returned for completeness. The process of entering the data is ongoing. Much of the data are optically scanned. If there are any unanswered questions in the baseline instrument or medical questionnaire, we ask the individuals to answer these questions over the phone.

Task 5: Final Data Analysis, Months 47-51

a. Perform all exploratory analyses to test for adherence to model assumptions.
b. Perform all data simplification tasks (e.g. principal components analysis).
c. Test study hypotheses.
d. Conduct post-hoc analysis of study data.
e. Prepare manuscripts.

In our first annual report we stated that except for e., preliminary data [Clemow, 1995 #1319; Massion, 1995 #1390] and theoretical considerations [Hebert, 1996 #1391], were reported.

In the second year two book chapters have been written where BRIDGES is discussed. The first book chapter is in the Textbook of Psycho-oncology [Kabat-Zinn, 1997 #2044]. The book chapter describes the SR&RP intervention and its application in oncology. BRIDGES is mentioned as an ongoing study. No data is provided from the BRIDGES study; it is mainly descriptive.

The second book chapter is in Melatonin in Psychiatric and Neoplastic Disorders [Massion, 1997 #2045]. The book chapter discusses our hypotheses about melatonin and meditation. BRIDGES is discussed and preliminary data are provided.

We also presented an abstract at the Society for Behavioral Medicine meeting in April, 1997. This was a preliminary report (n = 75) of baseline and four month scores on psychosocial measures. This abstract is attached as an appendix.

James Hebert was invited by the editor of Advances to provide comments to an article written by Keith Block. Dr. Block runs an alternative cancer treatment center in Illinois. Dr. Hebert provides an epidemiologist's view of Block's challenge by discussing his role as a reviewer of Department of Defense breast cancer grant applications and the grant application review process. BRIDGES is briefly mentioned [Hebert, 1997 #1681].

Lynn Clemow presented at a breast cancer conference in September sponsored by the Cancer Center of the University of Massachusetts Medical Center. This was a preliminary report (n=157) of baseline and four month and one year scores on psychosocial measures and dietary behavior. The abstract is attached as an appendix.

Ann Massion presented at a Symposium sponsored by the American Psychiatric Association on May 19, 1997. At this annual meeting she presented (n=75) baseline and fourth month data on psychosocial measures.

James R. Hebert also provided comments to an article written by Theodore Pincus "Analyzing Long-term Outcomes of Clinical Care Without Randomized Clinical Trials:

The Consecutive Patient Questionnaire Databases" [Hebert, 1997 #2065; Pincus, 1997 #1750].

We presented a poster at the Era of Hope Conference. Results presented were based on data from 157 women who have completed the 4-month assessment point. Both psychosocial and dietary behavior results are discussed. The abstract is attached as an appendix.

For the 1999 SMB Meeting, we have submitted two abstracts, one on change in dietary fat intake and body weight and one concerning intervention effects on health-related quality of life and psychological factors.

Numerous analyses are on-going. Both abstracts are presented in the Appendix.

Results

Psychosocial Well-Being: To date, the SRC intervention appears to produce the most consistent improvements in psychosocial well-being. The no-treatment control group (UC) appears to be associated with a slight deterioration and the NEP is associated with psychosocial outcomes intermediate between the SRC and UC groups. For example, we observed an increase of 1.4 vs. very little change (+0.7) in NEP and a reduction of -1.9 in UC ($p=0.0007$) in active-cognitive coping on the Dealing With Illness scale. Other variables which showed similar significant results for SRC are Depression (Beck and SCL-90-R), Spirituality (FACT-B), Helpless/hopeless thoughts (MAC), Emotional Expression (Courtauld scale), and emotional distress (SCL-90-R GSI and five subscales). Social support and Active-cognitive coping were significantly better in the NEP than UC group. The usual effect size (pre-post GSI on the SCL-90-R) for the standard UMass Stress Reduction Program in published studies in a variety of populations of self-selected participants (immediate treatment vs. wait-list controls) [Kabat-Zinn, 1982 #110; Kabat-Zinn, 1992 #114; Miller, 1995 #1386; Kabat-Zinn, 1986 #112] ranges from -0.25 to -0.57 (34-54% change). In this study, using an augmented version of the same program, the intervention produced a reduction of 0.12 (roughly 25% change) suggesting that the treatment effect might be larger in a design with Breast Cancer patients who select SRC instead of being randomly assigned to it.

At one-year follow-up, we found significant sustained benefits of the SRC condition on Spirituality, Active-Behavioral Coping and Emotional QoL on the overall sample.[Clemow, 1998 #2659] In an effort to explore the individual differences that may have modified the intervention effects (particularly those that might bear on the process of self-selection) we have conducted some preliminary subset analyses. Women with high baseline emotional distress (Beck Depression scores> median) were much more likely to benefit significantly at post-treatment and to have a more enduring effect after one year of the SRC vs. comparison conditions on a variety of psychosocial measures including : Higher Active-behavioral ($p=.01$) and Active Cognitive Coping ($p=.03$) and lower Avoidant Coping ($p=.008$); Less Helpless-Hopelessness ($p=.04$); higher Spirituality

(p=.01) and Emotional QoL (p=.005), higher social support (p=.003), and less distress on the GSI and 6 subscales of the SCL-90-R.(p=.05-.01).

Diet-Related Outcomes: Of all women randomized, 154 had complete baseline, 4-month (immediately post-intervention), and 12-month dietary data and 159 had body weight data for each time point. Though not focused on weight loss, we sought to examine change in weight partly because of the importance of weight as a prognostic indicator and partly as a construct validation of the dietary data. Changes in percent of energy as fat (%EF) and body weight (kg) were analyzed using PROC GLM in SAS, controlling for baseline value of the dependent variable. At 4 months, there were decreases of 5.6%EF and 1.3 kg in weight in the NEP versus slight increases in the SRC and UC (p=0.0002). At 12 months there was a slight rebound in fat intake in the NEP (4.5%EF less than baseline versus no change in the SRC or UC, p=0.008) but women had returned to their baseline weight. In 50% of women with high expectation there was a larger reduction in fat (-6.0%EF and –5.0%EF at 4 and 12 months, respectively, p<0.01), but the same pattern in terms of body weight change. The results of this study show that large reductions in dietary fat can be achieved in such an RCT and that the effect is larger in women who expect more of an effect from the intervention, indicating effect modification of the intervention by expectancy. Weight shows a pattern typical of many diet interventions, but it is notable that the weight gain typical of early-stage breast cancer patients was not observed [Demark-Wahnefried, 1997 #1855]. Both of these findings could translate to improved survival over time [Hebert, 1998 #1850].

Melatonin Excretion: Because we do not have complete data from the 4-month measurement point and no data, as yet, from the 2-year point, the following results are not presented as a formal test of the hypothesis that melatonin production (as estimated by excretion of its primary metabolite, urinary 6-sulphatoxymelatonin) changes with NEP or SRC, but in a more descriptive sense, broadly in support of pursuing the same study in the context of an SST. The assays are done in batches and as a result, 4-month samples from the last two intervention cycles have not been assayed as yet. Values presented are the least squares means of the change in melatonin (total *u*g/24 hours) between baseline and 4-months on the 125 women with paired data obtained using PROC GLM in SAS. All analyses controlled for baseline melatonin value. Overall, results were consistent with an increases in both the SRC (+1.21 *u*g/day) and NEP (+1.54) and a decrease in the UC (-0.38), but not close to "statistically significant" (p=0.49). In terms of magnitude of change, they are about one quarter to one half the size observed in our previous studies.

Additional analyses also considered surgical status (lumpectomy versus mastectomy), level of depression according to scores on the Beck Depression Inventory (BDI), Global Severity Index (GSI) from the SCL-90-R. and level of expectancy. Of the 105 women on whom we has paired melatonin data and data on surgical status, 84 (80%) had lumpectomies and 21 (20%) had mastectomies. While the relative (though technically non-significant) intervention effects persisted, the change in melatonin level between baseline and 4-months was significantly different between those with mastectomy (-2.50) and those with lumpectomy (+1.46) (p = 0.05). For women who were in the lower half

of depression, those in the SRC group appeared to have a larger change in melatonin level over the course of the intervention period than those in the other two groups: SRC = +3.55, NEP = -0.11, and UC = -1.16 ($p = 0.34$). Women above the 50th percentile score on the GSI (greater severity of symptoms), all showed either a decrease or minimal change in melatonin between baseline and 4 months, regardless of intervention group: SRC = -0.39, NEP = -2.13, and UC = -0.78 ($p = 0.82$). in this group, there appeared to be even larger differences according to surgical status: mastectomy = -3.50, lumpectomy = +1.29 ($p = 0.05$).

These results suggest that women given the SRC who have lower levels of depression are able to increase their melatonin production while the other two groups, NEP and UC, were not. Furthermore, the direction of change in melatonin according to intervention group was consistent with our hypothesis of increased melatonin for the SRC and NEP groups compared to the UC group and with results from two previous preliminary studies. In both of those studies, meditation practice was associated with a higher level of melatonin excretion. The magnitude of change observed here was less than half what was observed in those studies (about 1.2 vs. 2.3 to 5.8 *u*g/day), that a self-selection study in which the participants would presumably have higher motivation and level of practice, could show a greater change in melatonin level over the course of the intervention. As part of the BRIDGES RCT data management and analysis plan, we are in the process of assaying the remaining urine samples and developing additional analyses to take into account other variables, such as compliance with meditation practice and QoL.

CONCLUSIONS

In summary, progress of this grant has been excellent. We have received a no-cost extension for the following year. During this time period, we will continue to analyze the data along with performing the analyses on the cytokines. Recruitment ended in December 1996 with a total of 178 subjects (99% of the recruitment goal). Governance for the study has worked very well with most executive decision making happening in a small working group consisting of Drs. Hebert and Massion and Ms. Susan Druker. In some instances our decisions are provisional on their being broadcast to investigators at UMMC and other sites for final approval. Day-to-day operational issues have been decided mainly in the site coordinator's working group which is chaired by the Project Coordinator/UMASS Site Coordinator, Ms. Susan Druker. Because Susan Druker is a member of both of the functioning working groups, communications within UMMC site and across the four sites have been extraordinarily smooth and efficient. The overall Steering Committee Meeting has met two times in each of the years of the study. Occasionally, an executive decision has come out of these meetings. However, it has transpired that its main purpose is to provide information to investigators at the other sites and to rekindle enthusiasm in the study. Although there was no place to mention this above, it should be noted that the enthusiasm level for study and the dedication about which people feel regarding their own involvement and involvement in their patients has never been higher in any study with which I have been involved.

One of our major concerns in designing this study concerned issues around the asymmetry of intervention conditions where blinding is not possible. In the years of meetings before we formally proposed this study, we spent more time on this issue than anything else. Our concern was that an obvious imbalance between the intervention conditions would either lead to a low recruitment rate or there would be large differential dropout after women were randomized. With recruitment completed and having needed the interventions, we can confidently say that this has not been a problem.

I appreciate the opportunity to convey the excellent progress that we have had to date.

REFERENCES

Massion AO, Teas J, Hebert JR, Wertheimer MD, Kabat-Zinn J. Meditation, melatonin, and breast/prostate cancer: hypothesis and preliminary data. Medical Hypotheses 1995;44:39-46.

Levy SM, Herberman RB, Lippman M, D'Angelo T, Lee J. Immunological and psychosocial predictors of disease recurrence in patients with early-stage breast cancer. Behav Med 1991;17;67-75.

Hebert JR, Barone J, Reddy MM, Backlund JYC. Natural killer cell activity in a longitudinal dietary fat intervention trial. Clin Immunol Immunopathol 1990;54:103-116.

Hebert JR. An epidemiologist's view on the role of the self in cancer survival. Advances. In press 1997.

Clemow LC, Hebert JR, Lundquist D, Solomon J, Ennis F. Quality of life and immune variables in a group for young women with breast cancer. Annals of Behavioral Medicine 1995;17:177.

Hebert JR, Kabat GC, Ockene IS, Clemow L. Special problems in trials of behavioral and nutritional interventions: blinding and behavioral effect modification. In preparation 1996.

Kabat-Zinn J, Massion AO, Hebert JR, and Rosenbaum E. Meditation. In: Holland J (Ed.). Textbook of psycho-oncology. London: Oxford University Press, In press 1997.

Massion AO, Teas J, Hebert JR. Melatonin, meditation, and cancer. In: Shafii M and Shafii S (Eds.): Melatonin in psychiatric and neoplastic disorders. Washington, D.C.: American Psychiatric Press, Inc., In press 1997.

Personnel receiving pay from this effort:

James R. Hebert, Sc.D.
Lynn Clemow, Ph.D.
Sue Druker
Peter Fay
Jay Fowke
Tom Hurley
Nancy Saal
Barbara Olendzki
Janet Solomon
Noori Haeman
Ferris Urbanowski

DIETARY FAT AND BODY WEIGHT CHANGE IN EARLY STAGE BREAST CANCER FOLLOWING INTENSIVE DIETARY INTERVENTION: RESULTS OF A RANDOMIZED CLINICAL TRIAL

James R. Hebert, Sc.D., Lynn Clemow, Ph.D., Barbara C. Olendzki, R.D., Susan Druker, M.A., and Yunsheng Ma, M.D., M.P.H., University of Massachusetts Medical School

Dietary fat and correlated factors have been related to breast cancer survival, with benefits appearing to be largest in early stage disease and in younger women. In this study, a 16-session nutrition education program (NEP) was used as an attention control for testing the effectiveness of UMass Stress Reduction Clinic's (SRC) program on quality of life in women (< 65 years) newly diagnosed with early-stage breast cancer. A total of 162 women (mean age 50 years, 96% White) were randomized by stage (I or II), age, and clinic to SRC, NEP, or usual care (UC). Of these, 154 had complete baseline, 4-month (immediately post-intervention), and 12-month dietary data and 159 had body weight data.

Changes in percent of energy as fat (%EF) and body weight (kg) were analyzed using PROC GLM in SAS, controlling for baseline value. At 4 months, there were decreases of 5.6%EF ($p=0.0002$) and 1.3 kg in weight in the NEP ($p<0.01$) versus slight increases in the SRC and UC. At 12 months there was a slight rebound in fat intake in the NEP (4.2%EF less than baseline, $p<0.008$) but women had returned to their baseline weight. In 50% of women with high expectation, there was a larger reduction in dietary fat (-6.0%EF and –5.0%EF at 4 and 12 months, respectively, $p<0.01$), and a slight weight loss (1.6kg, $p=0.01$). The results of this study show that large reductions in dietary fat can be achieved in a randomized clinical trial and that the effect is larger in women who expect more of an effect. Weight change showed a pattern typical of many dietary interventions, but it is notable that the typical weight gain in early-stage breast cancer patients was not observed at 12 months. Both of these findings could translate into improved survival.

CORRESPONDING AUTHOR: James R. Hebert, Division of Preventive and Behavioral Medicine, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA, 01655, USA.

THE EFFECTS OF A MEDITATION-BASED STRESS REDUCTION PROGRAM IN WOMEN WITH EARLY-STAGE BREAST CANCER

Dr. James R. Hebert, Dr. Ann O. Massion, Dr. Lynn Clemow, Mr. Jay H. Fowke, Ms. Susan K. Druker, Dr. Judith K. Ockene, Dr. Jon Kabat-Zinn

University of Massachusetts Medical School
55 Lake Avenue, North, Worcester, MA 01655

The Breast Research Initiative for DeterminiG Effective Strategies (BRIDGES) for coping with breast cancer is a 51-month randomized multi-center trial to test the effect of the UMass Stress Reduction Clinic (SRC) program on quality of life, a variety of psychosocial factors, dietary intake, melatonin excretion, and circulating levels of cytokines. The three-arm study also consists of a no-treatment control group (UC) and a Nutrition Education Program (NEP), attentionally equivalent to the SRC and designed specifically for BRIDGES. The NEP excludes all aspects of meditation that form the basis of the SRC but includes aspects of group support, education, and dietary change that could influence some or all of the outcome variables. Recruitment ended in December 1996 with a total of 178 subjects, 99% of the recruitment goal of 180 younger women (to age 65 years) newly diagnosed with early-stage (I or II) breast cancer, and a retention rate >90% thus far. Subjects were randomized in equal numbers to each of the three study arms. Randomization was blocked by: stage of disease (I or II); age (<45, 46 to 52, or 53 to 65 years); and medical center. The last of six intervention cycles of the NEP and SRC were completed in April of 1997.

Data on study outcomes and a number of relevant background factors and potential confounders or effect modifiers of intervention effects were collected at baseline, 4 months (just after the end of the interventions), 12 months, and 24 months. Currently, we have data on 107 women who have completed the 4-month assessment point. Salient results are summarized in Table 1.

Keywords: Dietary Fat, Randomized Clinical Trial, Quality of Life, Affective Symptoms, Meditation

This work was supported by the U.S. Army Medical Research and Materiel Command under DAMD17-94-J-4475 and DAMD17-94-J-4261.

Table 1: Summary of Changes by Intervention

	UC		NEP		SRC		p-values[1]			
Psychosocial Variables:	base-line	Δ*	base-line	Δ*	base-line	Δ*	Overall	UC vs NEP	UC vs SRC	NEP vs SRC
Active-Cognitive Coping (Dealing with Illness)	62.1	-2.7	62.5	0	62.4	+1.0	0.005	0.03	<0.001	0.43
Quality of Life (FACT-B)	118.9	-1.0	117.5	-0.2	111.2	+3.6	0.60	0.87	0.33	0.45
Spirituality	29.1	-1.5	27.4	-0.3	26.3	+3.4	0.004	0.58	<0.001	0.01
Depression (Beck)	7.7	-1.6	6.1	-0.3	8.9	-2.8	0.11	0.45	0.15	0.04
Sense of Coherence	155.5	-4.1	155.2	-2.6	148.2	+3.2	0.21	0.70	0.09	0.22
Hostility (SCL-90)	0.26	+0.09	0.23	-0.02	0.29	-0.11	0.03	0.13	0.01	0.31
General Symptom Index (SCL-90)	0.38	-0.03	0.30	-0.01	0.47	-0.13	0.42	0.89	0.22	0.31
Nutritional Variables:										
fat (g/day)	69.7	-1.7	80.8	-21.1	71.6	+2.7	0.05	0.08	0.51	0.02
fat (% of energy)	33.75	-0.26	35.28	-7.26	34.85	+0.87	<0.001	<0.001	0.34	<0.001
energy (kcal/day)	1825	-48	2064	-199	1826	-2	0.42	0.78	0.76	0.57
weight (kg)	69.59	0.48	72.51	-1.59	72.85	-0.27	0.02	0.006	0.28	0.08

* differences are the crude differences observed

[1] p-values are based on the difference adjusted for the baseline values

Thus far, the SRC intervention appears to produce an improvement in the psychosocial factors. UC generally appears to be associated with a slight deterioration, and the NEP is associated with results intermediate between the SRC and UC. As can be seen in the table, large dietary changes were confined to the NEP. Though the NEP was not meant to be a weight loss program, successful low-fat interventions usually result in some weight loss. The loss of 1.59 kg (3.51 lbs) in the NEP would correspond to a decrease of about 13.3g of body fat per day, the equivalent of about 120 kcal of total dietary energy per day (about 60% of the reduction reported).

Results are consistent with the hypothesis that the SRC meditation approach would affect a range of psychosocial variables. The NEP intervention not only produces impressive results in terms of dietary change but is associated with results intermediate between the UC and SRC on several of the psychological variables. There appears to be no effect of age on any study outcome, indicating that the effects of the interventions apply to older women in whom the incidence rate of breast cancer is the highest. Other studies have shown that effects of such interventions may increase over time. Therefore, there will be considerable interest in monitoring intervention effects at the one- and two-year time points. Results presented will extend and expand upon those shown here and we will discuss their implications.

Dr. Lynn Clemow

The Effects of a Meditation-Based Stress Reduction Program in Women with Early-stage Breast Cancer

Lynn Clemow, Ph.D.
for the BRIDGES Study Group, James Hebert, Sc.D., PI

The Breast Research Initiative for determining Effective Strategies (BRIDGES) for coping with Breast Cancer is a 51-month randomized multi-center trial to test the effect of the UMass Stress Reduction Clinic (SRC) program and an attentionally equivalent Nutrition Education Program (NEP) on quality of life, a variety of psychosocial factors, dietary intake, melatonin, excretion, and circulating levels of cytokines. Recruitment ended in December, 1996 with a total of 178 subjects, 99% of the recruitment goal of 180 younger women (under age 65 years) newly diagnosed with early-stage (I or II) breast cancer, and a retention rate >90% thus far. Results presented here are the psychosocial and nutritional data, based on data from the entire sample who completed the 4-month assessment, and a series of the first 97 participants for whom we have 1-year assessments.

Overall thus far, the SRC intervention appears to produce improvements in a number of psychosocial factors. The no-treatment control group (UC) appears to be associated with a slight deterioration and the NEP produces results intermediate between the SRC and UC. These variables (from the 4-month data) include Active Cognitive Coping ($p=.005$), Spirituality ($p=.0007$), Beck Depression scores ($p = .02$), as well as several indices of emotional distress measured by the SCL-90-R, including anxiety ($p=.04$), Depression ($p=.01$), Hostility ($p=.01$), and the overall emotional distress scale ($p = .01$). Many of these beneficial differences hold up significantly at 1-year, as well.

Large dietary changes were confined to the NEP: for example, there was a reduction of 7.2% of energy as fat in the NEP vs no change in either the SRC or the UC ($p<0.001$). Though not meant to be a weight loss program, the NEP was associated with a loss of 1.59 kg ($p=0.02$). This corresponds to a decrease in body fat equivalent to about 120 kcal of total dietary energy per day (about 60% of the reduction in total energy reported).

Results were consistent with the hypothesis that the SRC meditation approach would affect a range of psychosocial variables. The NEP intervention not only produces impressive results in terms of dietary change but is associated with results intermediate between the UC and SRC on several of the relevant psychological variables.

ogy. This review will discuss studies on the emotional consequences of the following tests specific to breast cancer: 1) risk assessment for the BRCA1 gene, 2) screening mammography, 3) follow-up testing for recurrence of disease.

Patients tend to overestimate the utility of screening and diagnostic tests, and often incorrectly perceive the significance of a "normal" test. Individual variations in coping style appear to be a key factor in determining different psychological responses to receiving information. Prospective evaluations of quality of life and patients' perceptions of diagnostic interventions are needed, as well as physician training to assess and address the specific psychological needs of patients.

No. 14B
FERTILITY ISSUES IN WOMEN TREATED FOR BREAST CANCER

Randy S. Glassman, M.D., *Department of Psychiatry, Brigham & Women's Hospital, 75 Francis Street, Boston MA 02115;* Alison Fife, M.D.

SUMMARY:

For a woman of child-bearing age, a diagnosis of breast cancer carries both a physical and an emotional burden. The physical side effects of chemotherapy are numerous, and include potential effects on ovarian function, which affects fertility and sexual function, and may have implications for fetal anomalies. For example, female patients who have undergone bone marrow transplantation for acute myeloid leukemia have gone on to have successful pregnancies. Others developed ovarian failure and were unable to become pregnant. Infertility becomes an issue for these women, and carries with it the potential for comorbid psychological dysfunction for the patient, her partner, and family.

We review here the medical, ob-gyn, and psychiatric literature on fertility and the psychological and psychiatric issues in women who are anticipating or who have undergone treatment for breast cancer. The known effects of chemotherapy on ovarian function, and the available data on pregnancy outcomes will be reviewed. Additionally, the newer infertility treatments will be reviewed as they relate to decision making and psychological status. The potential for freezing embryos and possibly unfertilized eggs in the future will present women with new opportunities, but difficult and emotionally laden choices.

We will present information from interviews with women who have received chemotherapy for breast cancer, and who have either considered pregnancy or who have become pregnant. Psychiatric issues, comorbidity, and implications for treatment will be addressed.

No. 14C
MEASURING DEPRESSION IN WOMEN WITH BREAST CANCER

Mary Jane Massie, M.D., *Department of Psychiatry, Memorial Sloan-Kett, 1275 York Avenue, New York NY 10021-6007;* David K. Payne, Ph.D., Maria Theodoulou, M.D.

SUMMARY:

The most common types of psychological distress in women with breast cancer are depression and anxiety. Oncology staff members often ask consulting psychiatrists to recommend brief screening instruments that can be used to measure depression and anxiety and to assist them in learning how to rapidly identify patients most in need of psychiatric consultation. We have explored the use of two screening instruments (the Hospital Anxiety and Depression Scale [HADS] and a 100m visual analogue scale [VAS]) to measure psychological distress in 103 women with breast cancer and have explored correlations between patients' perceptions of their psychological distress and oncological staff members' perceptions of patients' psychological distress. The HADS tapped significant levels of distress that correlate with patients' subjective assessments of distress. The VAS correlated well with both the medical oncologist's and oncology nurse's ratings of the patients' distress, as well as with the HADS. The usefulness and limitations of brief screening measures to identify women with breast cancer who could benefit from psychiatric consultation will be described.

No. 14D
NEW RESEARCH IN PSYCHOSOCIAL INTERVENTIONS FOR WOMEN WITH EARLY-STAGE BREAST CANCER: THE BRIDGES STUDY

Ann O. Massion, M.D., *Department of Psychiatry, University of Mass Medical Ctr, 55 Lake Avenue North, Worcester MA 01655;* James R. Herbert, Sc.D., Lynn Clemow, Ph.D., M.D. Wertheimer, M.D., Jon Kabat-Zinn, Ph.D.

SUMMARY:

An increasing body of literature indicates that coping skills and psychosocial function can have an impact on quality of life and possibly recovery for women with breast cancer. There is a need to identify effective coping skills and cost-effective psychosocial interventions to facilitate coping with breast cancer. The BRIDGES study at the University of Massachusetts Medical Center was designed to address these issues. The study involves randomization to one of three arms: a meditation-based stress reduction intervention, a nutrition education intervention, and an individual approach group, which essentially is a usual-treatment group. Inclusion criteria are stage 1 or 2 breast cancer, age 65 or less, and within two years of diagnosis. Outcome variables include psychosocial measures (coping skills, quality of life, anxiety, and depression) and biological measures (immunological consisting of soluble Interleukin-2 receptor, Interleukin 4, and Interferon-gamma; and endocrinological consisting of the urinary melatonin metabolite, 6-sulphatoxymelatonin).

The presentation will include a brief literature review and presentation of preliminary data from the BRIDGES study (baseline and 4-month follow-up).

No. 14E
TREATING FAMILIES OF WOMEN WITH BREAST CANCER

Bonnie B. Greenberg, M.S.W., *Department of Social Work, Dana-Farber Cancer Institute, 44 Binney Street, Boston MA 02115*

SUMMARY:

Women being treated for breast cancer are faced with many challenges. Success in meeting these challenges is impacted by the reaction and involvement of the surrounding family/social system. This presentation will explore in detail the dimensions of family psychosocial assessment, unique breast cancer related issues, and appropriate psychosocial interventions.

A thorough, accurate assessment of the family's structure and dynamics is essential to effective intervention. Important areas of focus in assessing families with cancer include communication patterns, coping mechanisms, ability of members to support one another, individual and collective definitions of hope, potential role realignments, and pre-existing areas of family stress.

Family interventions should include the spouse/significant other, children, and/or parents/extended family, as much as is logistically possible. Treatment needs to be tailored to both the unique issues and developmental stages of the individual members as well as the